

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12Q 1/04, G01N 33/98	A1	(11) International Publication Number: WO 98/39470 (43) International Publication Date: 11 September 1998 (11.09.98)
(21) International Application Number: PCT/GB98/00510 (22) International Filing Date: 6 March 1998 (06.03.98) (30) Priority Data: 9704676.7 6 March 1997 (06.03.97) GB PCT/GB97/03543 27 December 1997 (27.12.97) WO (34) Countries for which the regional or international application was filed: GB et al. (71) Applicant (for all designated States except US): AROMAS-CAN PLC [GB/GB]; Electra House, Electra Way, Crewe, Cheshire CW1 1WZ (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): PAYNE, Peter, Alfred [GB/GB]; 16 The Stables, Tabley House, Tabley, Knutsford, Cheshire WA16 0HA (GB). PERSAUD, Krishna, Chandra [GY/GB]; 26 Wilmslow Road, Cheadle, Cheshire SK8 1NE (GB). SYMS, Allan, John [GB/GB]; 1 The Shires, King Street, Lach Dennis, Cheshire CW9 7FE (GB). (74) Agents: McNEIGHT, David, Leslie et al.; McNeight & Lawrence, Regent House, Heaton Lane, Stockport, Cheshire SK4 1BS (GB).		(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: DETECTION OF CONDITIONS BY ANALYSIS OF GASES OR VAPOURS (57) Abstract There is disclosed a method for detecting the occurrence of a condition in a respiring subject comprising the steps of: introducing emitted subject respiratory gases to a gas sensing device; detecting certain species present in said emitted subject respiratory gases with said gas sensing device; and correlating the presence of said species with the occurrence of the condition.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

DETECTION OF CONDITIONS BY ANALYSIS OF GASES OR VAPOURS

This invention relates to a method and apparatus for detecting the occurrence of a condition in a respiratory subject, in particular to a method which comprises detection of emitted respiratory gases.

It is known that the breath odour can provide an indication of certain conditions. A straightforward example is that of halitosis, or "bad breath". Another example is ketosis, wherein the presence of sweet smelling ketones and aldehydes in the breath can be an indication of diabetes.

The present invention provides a method and apparatus for detecting numerous conditions from the gaseous or volatile species present in breath. For the avoidance of doubt, the terms "gas" and "gases" are taken to comprise any species present in the gas phase, including vapours from volatile liquids.

According to a first aspect of the invention there is provided a method for detecting the occurrence of a condition in a respiring subject comprising the steps of:

introducing emitted subject respiratory gases to a gas sensing device;

detecting certain species present in said emitted subject respiratory gases with said gas sensing device; and

correlating the presence of said species with the occurrence of the condition.

- 2 -

The method is rapid, since the analysis is direct - there is no need to perform time consuming culturing steps. Furthermore, the method provides non-invasive clinical screening and monitoring of many conditions.

The respiring subject may be human.

The gas sensing device may comprise an array of semiconducting organic polymer gas sensors.

The gas sensing device may comprise a gas sensitive material, of which an electrical property may vary on exposure to gases. The gas sensitive material may comprise semiconducting organic polymer.

The gas sensing device may comprise a mass spectrometer or a GC-MS device.

The emitted respiratory gases may be obtained from a ventilator. In this way, on-line monitoring for the occurrence of a condition, or monitoring of the progress of a condition, is possible.

The emitted subject respiratory gases may be introduced directly to the gas sensing device.

The occurrence of an infection or a disease state may be detected.

The occurrence of a lung disorder may be detected, which may be pneumonia, tuberculosis or a yeast infection.

The occurrence of a gastrointestinal infection may be detected.

- 3 -

The occurrence of diabetes may be detected.

The presence of alcohol may be detected.

The occurrence of phenylketonuria may be detected.

According to a second aspect of the invention there is provided a detector for detecting the occurrence of a condition in a respiring subject comprising a gas sensing device and means for introducing emitted subject respiratory gases to the gas sensing device, which device is adapted to recognise the occurrence of a condition in the subject when certain species present in said emitted respiratory gases are detected.

The means for introducing emitted respiratory gases to the gas sensing device may comprise a ventilator.. The gas sensing device may be directly connected to the ventilator.

Methods and apparatus in accordance with the invention will now be described with reference to the accompanying drawings, in which:-

Figure 1 shows a first detector according to the invention;

Figure 2 shows a second detector according to the invention; and

Figure 3 shows response on a function of time for two patients presenting with pulmonary condition albicans.

The invention comprises a method for detecting the occurrence of a condition in a respiring subject comprising the steps of:

- 4 -

introducing emitted subject respiratory gases to a gas sensing device;

detecting certain species present in said emitted subject respiratory gases with said gas sensing device; and

correlating the presence of said species with the occurrence of the condition.

The method is primarily directed towards humans, although it will be apparent that it lends itself to the detection of conditions in many animals.

The gas sensing device 10 comprises an array 12 of semiconducting organic polymer gas sensors 14, the presence of gases being detected by monitoring variations in the dc resistances of said sensors 14. Such devices are manufactured, for example, by AromaScan plc, Crewe, UK. There are many semiconducting organic polymers suitable for such devices : examples include polypyrrole and polyindole and substituted variants thereof. It is a property of such polymer that the adsorption of certain (usually polar) gases causes measurable conductivity changes, and hence such gases may be detected by monitoring changes in the dc resistance of the polymer. Because each polymer typically exhibits quite broad band sensitivities, an array of gas sensors are employed. This permits selective identification of a wide range of gases by recognising the characteristic "fingerprint" of response across the array (see, for example, J V Hatfield, P Neaves, P J Hicks, K Persaud and P Travers, *Sensors & Actuators B*, 18-19 (1994) 221-228). The output of the sensors 14 is analysed by analysis means 22, which correlates the output pattern of sensor response with the occurrence of certain conditions. The analysis means 22 is usually a computer or microprocessor. A single such device can be used to recognise a number of conditions. The use of a trained neural network is particularly advantageous in this regard.

It is also possible to interrogate semiconducting organic polymers by applying an electrical signal thereto and monitoring an impedance quantity of the polymers, or variations in such an impedance quantity, as a function of the frequency of the applied ac electrical signal (see, for example, British Patent GB 2 203 553 and M E H Amrani, R M Dowdeswell, P A Payne and K C Persaud, Proceedings of Eurosensors X, Vol. 2, (1996) pp 665-668). Using this approach, a single semiconducting organic polymer sensor can provide information equivalent, or actually superior, to that provided by an array of such sensors interrogated by the dc resistance technique.

Other types of gas sensors which comprise a gas sensitive material might be employed, such as metal oxide semiconductor (MOS), quartz resonator or surface acoustic wave (SAW) devices. An array comprising a plurality of such devices would be utilised. Alternatively, a mass spectrometry or a GC-MS device might be used. Alternatively still, spectroscopic techniques such as infra-red spectroscopy might be employed.

Advantageously, the emitted subject respiratory gases are introduced directly to said gas sensing device 10. As shown in Figure 1, this might be accomplished by a subject 16 exhaling into a tube 18, the tube 18 being in communication with a region 20 containing the gas sensing device 10. The gas sensing device 10 might be purged with an inert gas, such as nitrogen, and a one-way valve might be positioned between the tube 18 and the gas sensing device 10, in order to retain the atmosphere of inert gas until the subject 16 exhales. Alternatively, the subject 16 may exhale into a receptacle, such as a bag, which is sealable so as to retain a headspace which may subsequently be introduced to the gas sensing device 10. The entire detector, comprising the gas sensing device 10 and the means 18 for introducing respiratory gases to the gas sensing device 10, might be provided as a portable, possibly hand-held device.

The emitted respiratory gases can be obtained from a ventilator. Figure 2 depicts such an arrangement, in which emitted respiratory gases are exhausted from the output 52a of a ventilator 52. An array of gas sensors 50 is directly connected to the output 52a of the ventilator, and thus continuously samples the respiratory gases of the subject. As described above, a single gas sensor might be provided. The gas sensing device is defined by the gas sensors 50, measurement means 54 for measuring the response of the gas sensors 50, and a computer 56, employed to control the overall gas sensing procedure and for data analysis purposes. It may be necessary to include filters or concentrators into the system. It is possible to reduce water content or to concentrate low levels of important volatiles using Tenax tubes, affinity columns and other purge and trap systems.

Example

Measurements were performed on the respiratory gases, obtained from ventilators, of two patients presenting with pulmonary candida albicans, using a thirty two sensor semiconducting polymer instrument (AromaScan A32S). Measurements of response patterns were made once a day over a period of five days.

Figure 3 shows the results in the form of a Sammon map (in which response patterns are reduced to a two dimensional coordinate), the rectangles 60 representing measurements of the respiratory gases of a first patient, and the triangles 62 representing measurements of the respiratory gases of a second patient. The data obtained from the second patient are quite stable, the response patterns being grouped in a tight cluster. This correlates with the fact that the patient was very stable, subsequently making an excellent recovery. In contrast, the response patterns obtained from the first patient vary greatly from day to day. This correlates with the fact that the patient was very unstable, and died on the fifth day of measurements.

There are numerous conditions which may be detected using the method of the present invention. Examples include lung disorders, such as pneumonia, lung cancer, tuberculosis or yeast infections such as candida albicans, and gastrointestinal infections, such as those caused by helicobacter. Additionally, diabetes may be detected via a patient's breath, due to the presence of characteristic aldehydes and ketones, and the presence of alcohol in the patient's system can be detected by detecting same in the breath. Halitosis is also detectable, as is the occurrence of the liver disorder PKU (phenylketonumia). The latter is at present detected via urine tests. Other infections or disease conditions, such as heart disease, might be detectable. The technique may be used for screening purposes, for example in pre-clinical trials or in the detection of drugs.

When monitoring is performed on-line using a ventilator, it is possible to interface the system to a drug delivery system so that optimal quantities of antibiotics or other drugs are administered. It is possible to select which drugs are administered depending on the analysis performed on the respiratory gases. Alternatively, or additionally, data fusion is possible in which the data provided by the present invention is combined with data from other sources, such as temperature, blood pressure, carbon dioxide levels, oxygen levels, data on anaesthetic gases and data on blood chemistry, to provide a vital signs index.

CLAIMS

1. A method for detecting the occurrence of a condition in a respiring subject comprising the steps of:

introducing emitted subject respiratory gases to a gas sensing device;

detecting certain species present in said emitted subject respiratory gases with said gas sensing device; and

correlating the presence of said species with the occurrence of the condition.

2. A method according to claim 1 in which the subject is a human.

3. A method according to claim 1 or claim 2 in which the gas sensing device comprises an array of gas sensors.

4. A method according to any of the previous claims in which the gas sensing device comprises a gas sensitive material.

5. A method according to claim 4 in which an electrical property of the gas sensitive material varies on exposure to gases.

6. A method according to claim 5 in which the gas sensitive material comprises semiconducting organic polymer.

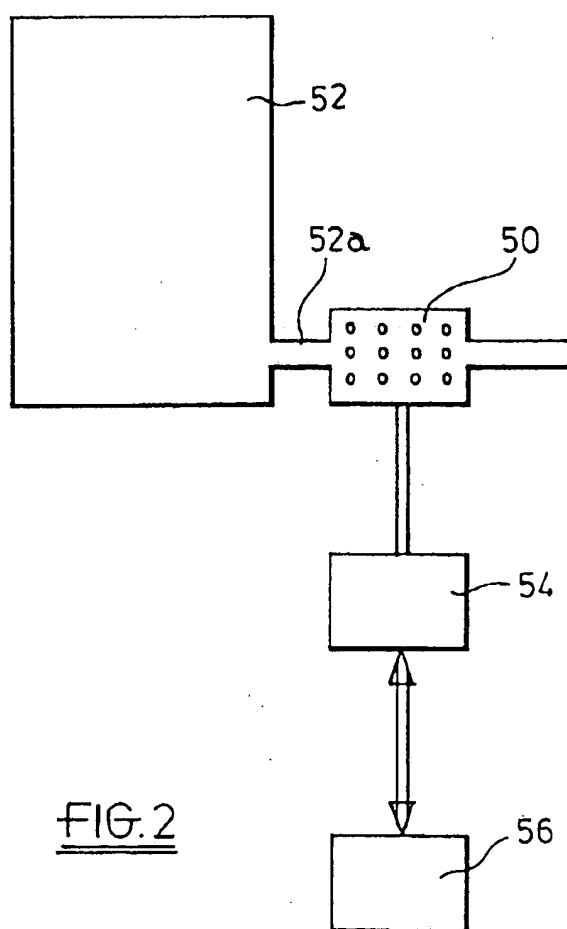
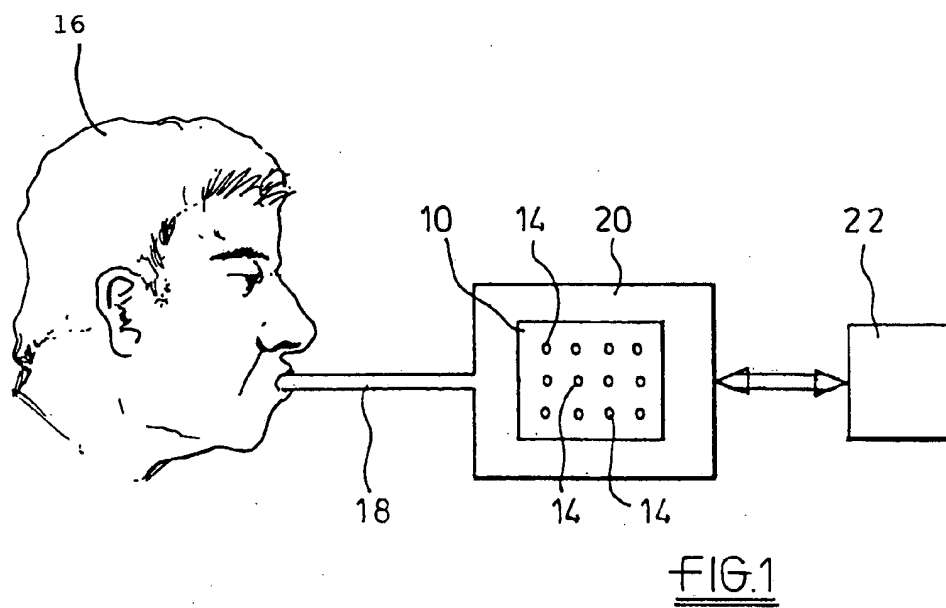
7. A method according to claim 1 or claim 2 in which the gas sensing device comprises a mass spectrometer or a GC-MS device.

8. A method according to any of the previous claims in which the emitted respiratory gases are obtained from a ventilator.
9. A method according to any of the previous claims in which the emitted subject respiratory gases are introduced directly to said gas sensing device.
10. A method according to any of the previous claims in which the occurrence of an infection or a disease state is detected.
11. A method according to any of claims 1 to 10 in which the occurrence of a lung disorder is detected.
12. A method according to claim 11 in which the lung disorder is pneumonia, tuberculosis or a yeast infection.
13. A method according to any of claims 1 to 10 in which the occurrence of a gastrointestinal infection is detected.
14. A method according to any of claims 1 to 10 in which the occurrence of diabetes is detected.
15. A method according to any of claims 1 to 10 in which the presence of alcohol is detected.
16. A method according to any of claims 1 to 10 in which the occurrence of phenylketonuria is detected.
17. A detector for detecting the occurrence of a condition in a respiring subject comprising a gas sensing device and means for introducing emitted subject respiratory

gases to the gas sensing device, which device is adapted to recognise the occurrence of a condition in the subject when certain species present in said emitted respiratory gases are detected.

18. A detector according to claim 16 in which the means for introducing respiratory gases to the gas sensing device comprises a ventilator.

19. A detector according to claim 18 in which the gas sensing device is directly connected to the ventilator.



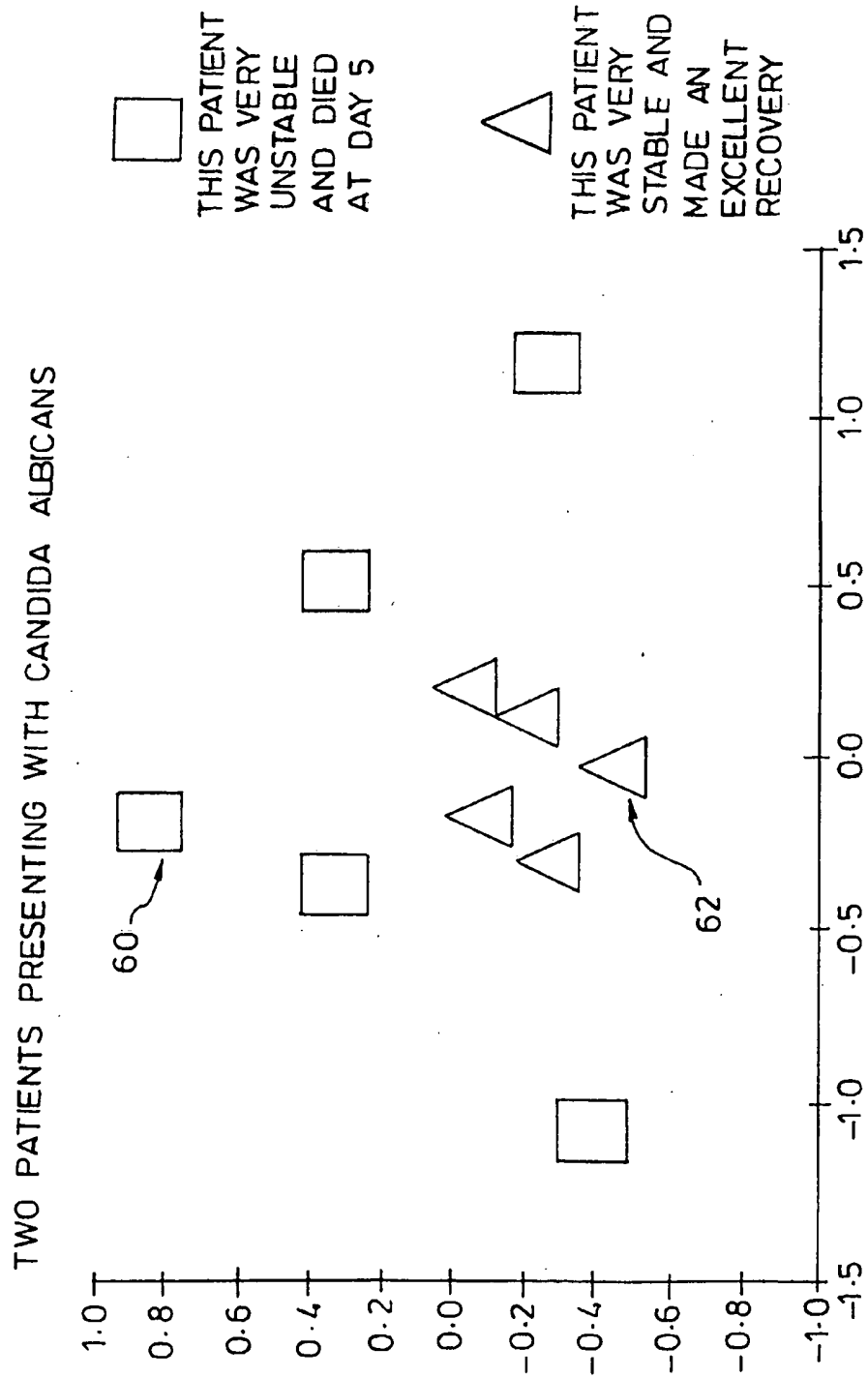
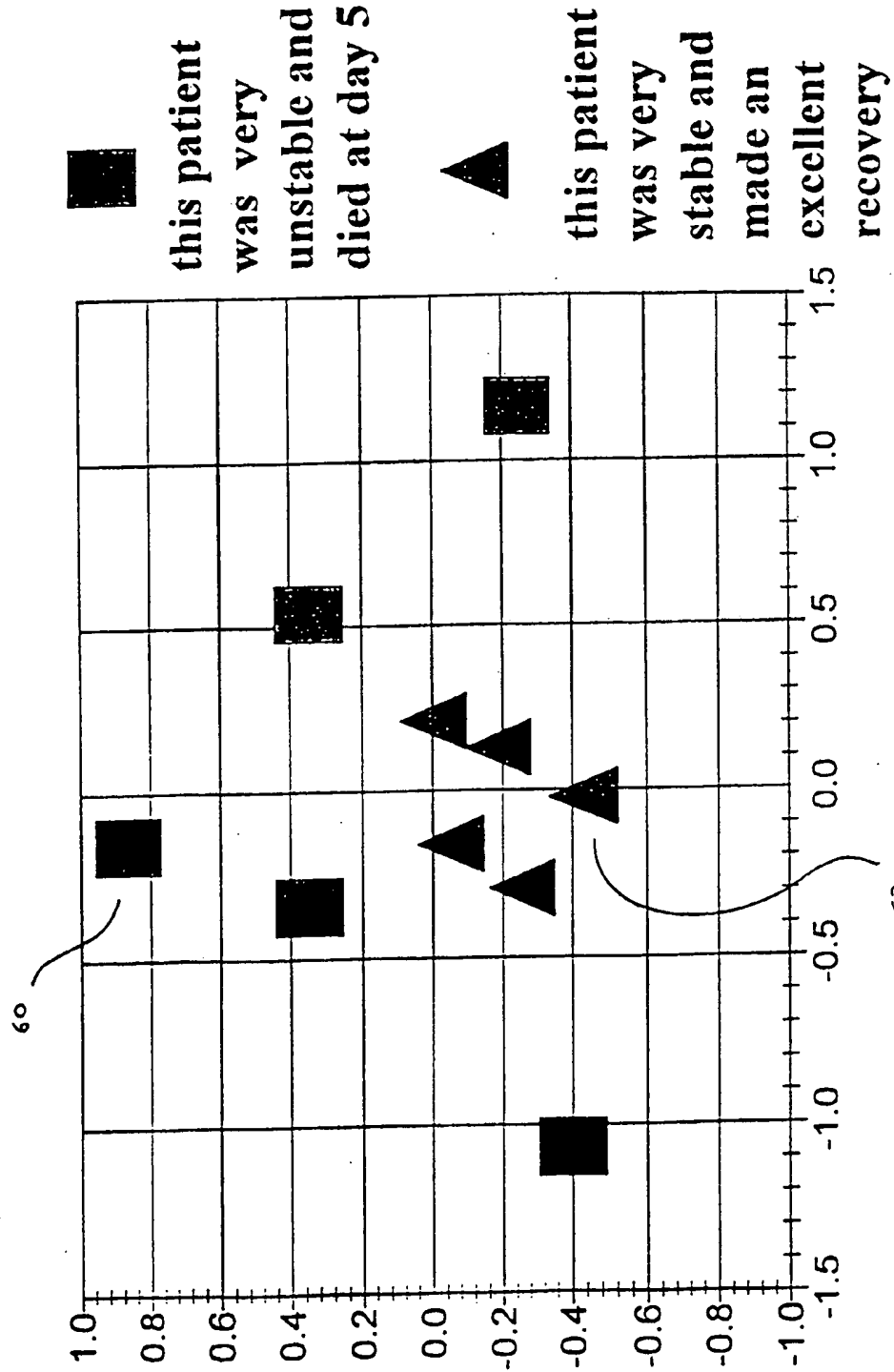


FIG. 3

3/3

Fig. 3

Two patients presenting with *Candida albicans*



62

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/00510

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q1/04 G01N33/98

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 33848 A (P.A. PAYNE ET AL.) 14 December 1995	1-16, 18, 19
X	see the whole document	17
Y	PATENT ABSTRACTS OF JAPAN vol. 96, no. 4, 30 April 1996 & JP 07 323034 A (HITACHI LTD), 12 December 1995, see abstract	1-16, 18, 19
A	WO 94 04705 A (THE MINISTER OF AGRICULTURE FISHERIES AND FOOD OF THE UNITED KINGDOM) 3 March 1994 see the whole document	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 April 1998

Date of mailing of the international search report

29/04/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Van Bohemen, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/00510

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9533848 A	14-12-95	AU 2678095 A EP 0765399 A JP 10501124 T	04-01-96 02-04-97 03-02-98
WO 9404705 A	03-03-94	AU 4967493 A EP 0656066 A	15-03-94 07-06-95